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The McCune-Albright syndrome: a lethal gene surviving by mosaicism

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In the McCune-Albright syndrome, fibrous dysplasia of bones and various forms of endocrine dysfunction are associated with multiple pigmented skin lesions. Examination of a 4-year-old female patient and comparison with photographs published in the literature revealed that the cutaneous pigmentation is arranged in a systematized pattern following the lines of Blaschko. Apparently, this pattern visualizes the dorso-ventral outgrowth of two different populations of cells during early embryogenesis. As all cases of the syndrome are sporadic, it is postulated that the disease is caused by an autosomal "dominant" lethal gene, leading to loss of the zygote in utero. Cells bearing the mutation can only survive when they are intermingled with normal cells. The mosaic may arise either from a gametic half chromatid mutation, or from an early somatic mutation. This concept offers an explanation for the scattered asymmetric distribution of bone lesions, and for the observation that the endocrinopathy may be either of central or peripheral origin, according to the random distribution of the mutant population of cells.

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The McCune-Albright syndrome is characterized by the triad of polyostotic fibrous dysplasia, cutaneous pigmentation, and endocrine dysfunction resulting in sexual precocity (McKusick 1983, No. 17480). The clinical signs and symptoms are very variable, and incomplete forms of the syndrome may occur (Grant & Martinez 1983). The etiology of the disease is unknown. There is no evidence of a hereditary basis since there is no convincing report of a family observation, except a report on monozygotic twins (Lemli 1977). Here the concept is proposed that the syndrome is caused by a dominant lethal gene defect surviving by mosaicism.

Etiological Concept

Evidence for Cutaneous Mosaicism

The pigmented lesions of the McCune-Albright syndrome have been described as café-au-lait spots with an irregular outline and irregular topography. Many authors have noted that the skin lesions display a linear or "segmental" distribution (Boenheim & McGavack 1952, Benedict et al. 1968, Warkany 1971), and that they often show a unilateral arrangement, strictly respecting the ventral midline (Frenk 1971, Ortonne et al. 1980).

One important fact, however, has not been noticed by previous authors. When

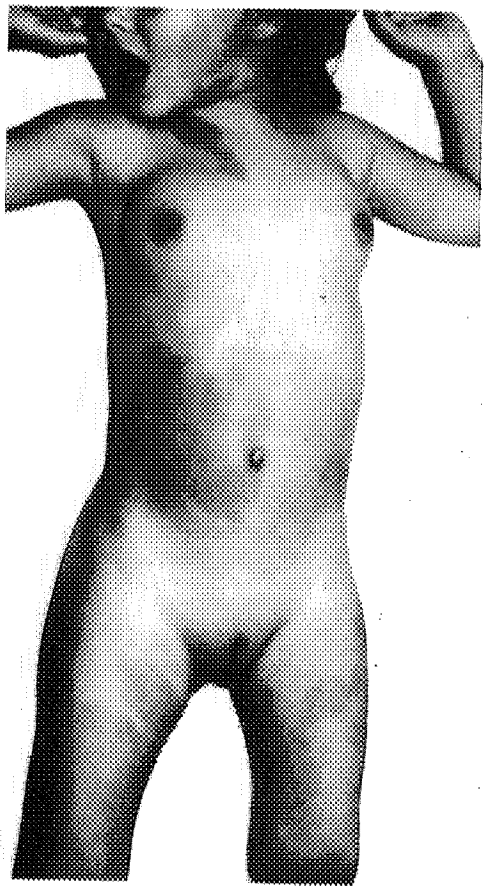

Fig. 1. Linear and patchy pattern of pigmented skin lesions suggesting mosaicism in a four-year-old girl affected with the McCune-Albright syndrome. Note the S-figure of uninvolved skin within the area of pigmentation on the right side of the abdomen. Sexual precocity was noted during the first months of life when regular menstrual periods began.

examining a four-year-old girl affected with the disease, I had the impression that the areas of pigmentation followed the lines of Blaschko (1901) (Fig. 1). An evaluation of photographs published by other authors confirmed this assumption. The typical fountain-like, V-shaped pattern on the back has been documented by Benedict et al. (1968) and Pierini et al. (1981). Evidence for the characteristic S-shape on the lateral and anterior aspects of the trunk has been provided by Albright et al. (1938), Benedict et al. (1968) and Ortonne et al. (1980). On the extremities, a perpendicular pattern of linear lesions has been documented by Strassburger et al. (1951) and Warkany (1971). The pattern of the lines of Blaschko was less conspicuous but still discernible on photographs published by Aarskog & Tveteraas (1968), Gorlin et al. (1976) and Smith (1982).

As a general rule, nevoid skin lesions following the lines of Blaschko visualize the dorso-ventral outgrowth of two different populations of cells during early embryogenesis, thus reflecting mosaicism (Happle 1978). As patients suffering from the McCune-Albright syndrome show this cutaneous pattern, it is likely that their organism is composed of two different cell clones.

Evidence for Lethality of the Gene

If the cutaneous mosaicism would be merely functional, as proposed in several other skin disorders arranged in a pattern following the lines of Blaschko (Happle 1985), one would expect that the McCune-Albright syndrome should be a hereditary trait. All cases, however, are sporadic, and this is best explained by the action of a "dominant" lethal gene, killing the embryo during its development. Cells bearing this mutation would be able to survive only in a mosaic state, in close proximity with normal cells. (The same mechanism of origin may apply to several other sporadic syndromes showing a mosaic distribution of anomalies. For obvious reasons, this mosaic pattern will be most easily detected when the underlying gene defect involves the skin.)

Mechanisms Which May Give Rise to the Mosaic

The mosaic pattern observed in the

McCune-Albright syndrome may be produced either by a gametic half chromatid mutation, as first assumed for incontinentia pigmenti in males by Lenz (1975), or by an early somatic mutation. A unilateral or even more circumscribed involvement would result from a mutation occurring at a later time in embryogenesis.

Applicability and Relevance of the Concept

What can be learned from this concept for the understanding of the various clinical features of the McCune-Albright syndrome?

First, this theory explains the scattered and asymmetric distribution of bone lesions, including the marked asymmetry of the face (Delacrétaz & Rutschmann 1960, Firat & Stutzman 1968).

Second, the concept of mosaicism explains the protean variability of endocrine disturbances observed in this syndrome (DiGeorge 1975). In the past, there was a controversy as to whether the endocrine dysfunctions are mediated by hypothalamic-pituitary mechanisms (Hall & Warrick 1972, Lightner et al. 1975, Chung et al. 1983), or result from autonomous activity of peripheral glands (Danon et al. 1975, Giovannelli et al. 1978, D'Armiento et al. 1983). The proposed concept implies that both mechanisms are possible, depending on the random distribution of mutant cells within the endocrine glands. This view is supported by the histological demonstration of a mosaic distribution of abnormal cells within endocrine glands (Kovacs et al. 1984), and by the clinical observation that sexual precocity may be arrested by unilateral ovariectomy (Pray 1951).

Third, this concept explains the occurrence of incomplete forms of the syndrome (Grant & Martinez 1983, Lorini et al. 1984) which would be attributed to a minor proportion of mutant cells within the mosaic.

Fourth, mosaicism resulting from a gametic half chromatid mutation may explain the simultaneous occurrence of this nonhereditary trait in monozygotic twins (Lemli 1977). The twins differed with regard to the degree of involvement, and this would be due to a random distribution of the mutant cells.

Conclusion

In the McCune-Albright syndrome, both male and female patients are able to have offspring. For the practical purpose of genetic counseling, the action of a lethal gene would explain why the risk of recurrence is not increased for the patients' sibs and children. The concept would imply that affected women should have an increased rate of abortions. The loss of the zygote, however, may already occur at the time of implantation and thus remain unnoticed. Special attention should be given to this question in further clinical studies.

Moreover, if the concept of mosaicism holds true, an *in vitro* comparison of the two different populations of cells may help to further elucidate the underlying gene defect.

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